

### REMARKS

Applicant has amended claims 26 and 27 to incorporate claims 11 and 33, respectively, and to remove the previously recited range of dosages. Applicant also has amended claim 12 to depend from claim 26. Claims 9, 10, 11, 33, and 34 have been canceled. No new matter has been added by these amendments.

Applicant also has added new claims 41-56, which relate to a method for stimulating the immune system of a human patient, wherein the method includes administering an immunostimulatory dosage of an  $\alpha$ -interferon composition to a patient, determining whether the natural killer lymphocyte cytotoxicity of the patient is increased at least about 75% above a baseline level of natural killer lymphocyte cytotoxicity in the patient, and administering an adjusted immunostimulatory dosage of  $\alpha$ -interferon if the natural killer lymphocyte cytotoxicity is not at least about 75% above the baseline. Support for new claims 41-56 can be found throughout Applicant's specification. For example, the specification at page 4, lines 2-5 discloses that an immunostimulatory dosage can increase a patient's NK lymphocyte cytotoxicity at least about 75% above the level of NK lymphocyte cytotoxicity level in the patient prior to administration of  $\alpha$ -interferon. Moreover, the Examples (e.g., Example 4) of Applicant's specification disclose a method for treating an individual with an  $\alpha$ -interferon composition, measuring NK lymphocyte cytotoxicity, and adjusting the dosage of  $\alpha$ -interferon if the level of cytotoxicity not sufficiently increased relative to the baseline. Thus, no new matter has been added.

In light of these amendments and the following remarks, Applicant respectfully requests reconsideration and allowance of claims 8, 12, 18, 21-22, 26-27, 30-32, 35-38, and 41-56.

#### Telephonic Interview

Applicant's agents thank Examiner Holleran for the courtesy of a telephone interview on July 23, 2004. Applicant appreciates the Examiner's suggestion to incorporate dependent claims 11 and 33 into claims 26 and 27, respectively.

Rejections under 35 U.S.C. § 103

In the Final Office Action mailed January 28, 2004 and the Advisory Action mailed July 7, 2004, the Examiner maintained the rejection of claims 26, 8-12, 18, 21, and 22 under 35 U.S.C. § 103(a) as being unpatentable over Tovey *et al.* (U.S. Patent No. 5,997,858) in view of Brittenden *et al.* (*Cancer* 77:1226-1243, 1996). The Examiner stated that the Tovey *et al.* patent teaches methods that include administering  $\alpha$ -interferon, but fails to teach a method that includes determining NK cell cytotoxicity. The Examiner further stated that the Brittenden *et al.* reference teaches that  $\alpha$ -interferon enhances NK cell activity, and that NK cell activity plays an important role in natural cytotoxicity of cancer cells. Thus, the Examiner alleged that it would have been *prima facie* obvious to one of ordinary skill in the art to add steps of measuring NK cell cytotoxicity to the methods disclosed in the Tovey *et al.* patent.

Amended claim 26 recites a method for stimulating the immune system of a human patient having a non-resectable malignant tumor, wherein the method includes determining the baseline natural killer lymphocyte cytotoxicity of the patient, administering an immunostimulatory dosage of an  $\alpha$ -interferon composition that increases NK lymphocyte cytotoxicity at least about 75% above the baseline level of cytotoxicity, and treating the patient with non-surgical medical methodologies to diminish the tumor. As amended, claim 26 is patentable over the cited references. The Tovey *et al.* patent discloses methods for treating neoplastic disease by administering an interferon. The Tovey *et al.* patent also discloses particular dosages that can be administered to a mammal in order to achieve a therapeutic effect (i.e., increased length of survival) without a pathological response. The Brittenden *et al.* reference teaches that  $\alpha$ -interferon enhances NK cell activity, and that cytotoxicity mediated by NK cells plays a role in host anti-cancer defense mechanisms. At no point, however, does the Tovey *et al.* patent or the Brittenden *et al.* reference suggest determining a baseline level of NK lymphocyte cytotoxicity in a patient. Moreover, neither reference suggests administering to a patient a dose of  $\alpha$ -interferon that increases the NK lymphocyte cytotoxicity to a particular level, let alone to a level that is at least about 75% above a baseline level. Thus, the combination the Tovey *et al.* patent with the Brittenden *et al.* reference does not suggest the presently claimed method. In fact, a person having ordinary skill in the art, reading the cited references at the time Applicant filed, would not have been motivated to determine the baseline NK lymphocyte

cytotoxicity in a patient and then administer to the patient a dose of  $\alpha$ -interferon that would increase the level of NK lymphocyte cytotoxicity at least about 75% above the baseline. As such, the combination of the Tovey *et al.* and Brittenden *et al.* references fails to render the present claims obvious.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 26, 8, 12, 18, 21, and 22 under 35 U.S.C. § 103(a).

The Examiner also maintained the rejection of claims 27 and 30-38 under 35 U.S.C. § 103(a) as being unpatentable over Markovic *et al.* (*Int. J. Cancer* 45:788-794, 1990) in view of the Tovey *et al.* patent (*supra*). The Examiner stated that the Markovic *et al.* reference teaches that  $\alpha$ -interferon acts to increase NK lymphocyte cytotoxicity, which is desired in the surgical treatment of cancer. The Examiner further stated that the Markovic *et al.* reference teaches a method for surgical removal of tumors from mice treated with  $\alpha$ -interferon prior to surgery. In addition, the Examiner stated that while the Markovic *et al.* reference fails to teach either methods for treating humans or dosages of  $\alpha$ -interferon that increase NK lymphocyte cytotoxicity by at least 50% or at least 75%, the Tovey *et al.* patent teaches dosages of  $\alpha$ -interferon in humans that stimulate the immune system. The Examiner further alleged that it would have been *prima facie* obvious to one of skill in the art to combine the teachings of the Markovic *et al.* reference with the teachings of the Tovey *et al.* patent to devise a method for treating humans.

Amended claim 27 recites a method for stimulating the immune system of a human patient having a resectable malignant tumor, wherein the method includes determining the baseline natural killer lymphocyte cytotoxicity of the patient, administering to the patient an immunostimulatory dosage of an  $\alpha$ -interferon composition that increases natural killer lymphocyte cytotoxicity at least about 75% above the baseline level of cytotoxicity, and surgically resecting the malignant tumor. As amended, claim 27 is patentable over the cited references. The Markovic *et al.* reference discloses the use of a mouse tumor model to show that administration of interferon prior to excision of a primary tumor can reduce dissemination and/or metastasis, and thus increase survival. The teachings of the Tovey *et al.* patent have been discussed above. At no point does either of these references suggest determining a baseline level

of NK lymphocyte cytotoxicity. Furthermore, at no point does either reference suggest administering to a patient a dose of  $\alpha$ -interferon that increases NK lymphocyte cytotoxicity to a particular level, let alone to a level that is at least about 75% above a pre-determined baseline level. Thus, a person having ordinary skill in the art, reading the Markovic *et al.* reference and the Tovey *et al.* patent at the time the present application was filed, would not have been motivated to combine the teachings of these references to arrive at the presently claimed methods. As such, this combination of cited references fails to render the present claims obvious.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 27, 30-32, and 35-38 under 35 U.S.C. § 103(a).

### CONCLUSION

Applicant submits that claims 8, 12, 18, 21-22, 26-27, 30-32, 35-38, and 41-56 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned if such would further prosecution. Enclosed is a check for the third month of the Petition for Extension of Time fee and for excess claim fees. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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